Effects of oral bisphosphonates on myopic choroidal neovascularisation over 2 years of follow-up: comparison with anti-VEGF therapy and photodynamic therapy. A pilot study

Akiko Miki, Shigeru Honda, Takayuki Nagai, Yasutomo Tsukahara, Akira Negi

Department of Surgery, Division of Ophthalmology, Kobe University Graduate School of Medicine, Kobe, Japan

Correspondence to
Dr Shigeru Honda, Department of Surgery, Division of Ophthalmology, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan; sighonda@med.kobe-u.ac.jp

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ABSTRACT

Background Choroidal neovascularisation is often associated with pathological myopia. Bisphosphonates (BP), the preferred drug for treatment of osteoporosis, are known to have anti-angiogenic effects.

Objective To compare the therapeutic effects of oral BP with anti-vascular endothelial growth factor therapy (anti-VEGF) and photodynamic therapy (PDT) for myopic choroidal neovascularisation (mCNV) over 2 years of follow-up.

Methods One hundred eyes of 96 consecutive patients with mCNV who underwent oral BP treatment (alendronate 5 mg/day or 35 mg/week), anti-VEGF therapy, PDT or observation only were followed up for 2 years. The best-corrected visual acuity (BCVA) and the central retinal thickness (CRT) in optical coherence tomography were compared among the treatment groups.

Results The mean BCVA of the patients was maintained for up to 2 years in the BP and PDT groups. In the anti-VEGF group, the mean BCVA was significantly improved but was significantly worse in the no-treatment group. The visual outcomes were significantly better in the BP, PDT and anti-VEGF groups than the no-treatment group over 2 years of follow-up (−0.28, −0.26 and −0.39 logMAR units, p=0.032, 0.021 and 0.0004, respectively). The mean CRT was significantly decreased in all treatment groups (−84, −121 and −122 mm, p=0.0025, 0.017 and 0.000025, respectively).

Conclusions Oral BP should be investigated further as possible therapeutic and preventive drugs for mCNV.

INTRODUCTION

Pathological myopia is the leading cause of choroidal neovascularisation (CNV) in people under 50 years old.[1] Patients with pathological myopia are common in Asian populations, including the Japanese population, and the number of patients has increased over the years. Myopic choroidal neovascularisation (mCNV) is a major complication of pathological myopia, which has a poor prognosis in its natural course; the visual acuity decreases to less than 20/200 in 89% of the eyes after 5 years.[2]

Recently, a number of studies have reported that intravitreal injections of recombinant humanised monoclonal antibodies against vascular endothelial growth factor (VEGF), such as bevacisumab or ranibizumab, are effective against mCNV.[3] However, repeated injections of anti-VEGF agents are needed to keep the lesion stable and to maintain vision, with one report indicating that a mean of 2.5 injections of ranibizumab or 4.7 injections of bevacizumab were required over 18 months of follow-up.[4] These re-treatments may pose a cumulative risk of ocular and systemic complications such as endophthalmitis and strokes,[5–7] and are a burden for patients and healthcare systems. Hence, we were interested in finding alternative treatments using oral drugs or eye drops, which are usually less expensive, easier to use and may also be used for prevention.[8]

Bisphosphonates (BP) are powerful inhibitors of osteoclasts, and are the preferred drug for treatment and prevention of osteoporosis.[9] Studies have shown that the anti-tumor and anti-angiogenic effects induced by suppressing VEGF expression are associated with BP, which suggests new areas of research for these drugs in tumorigenesis and angiogenesis.[10–12] However, in ophthalmology, BP are known only as drugs that may cause uveitis, scleritis or orbital inflammation as rare side effects.[13 14] BP were thought to accumulate mostly in bone tissue, but we suspected that they might have good permeability into the eye, possibly even causing side effects in rare cases. We have shown that BP have inhibitory effects on laser-induced CNV in mice, with suppression of VEGF expression.[15] Recently, we also carried out a preliminary study of the therapeutic effects of BP in human CNV associated with age-related macular degeneration and pathological myopia.[16]

In this study, we have assessed the visual outcomes of oral BP treatment in mCNV, and compared them with those of anti-VEGF therapy, photodynamic therapy with verteporfin (PDT) and natural course over 2 years of follow-up.

METHODS

One hundred eyes from 96 consecutive patients with treatment-naïve mCNV referred to Kobe University Hospital from May 2000 to February 2011 were included in the study.

CNV was determined by slit-lamp biomicroscopies of the fundi, colour fundus photographs, optical coherence tomography (OCT) (Stratus or Cirrus OCT, Carl Zeiss Meditec Japan, Tokyo, Japan), fluorescein angiography and indocyanine green angiography. Pathological myopia was diagnosed by an axial length ≥26.5 mm or uncorrected refractive error ≤−6.0 dioptres with the corresponding fundus findings. All cases of mCNV included subretinal lesions accompanied by subretinal haemorrhages. Table 1 summarises the clinical

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Table 1 Clinical data summary of the enrolled patients

Clinical data	Anti-VEGF (n=37)	PDT (n=20)	BP (n=21)	No treatment (n=22)	p Value
Gender (male/female)	10/27	3/17	2/15	5/17	0.40*
Age (years)	60.3±14.2	66.9±6.9	65.9±8.5	62.8±9.5	0.73†
Refractive error (D)	−12.0±4.0	−11.6±4.6	−12.1±4.7	−12.2±3.4	0.98†
Axial length (mm)	29.2±1.7	28.8±1.4	28.5±1.2	29.1±1.6	0.48†
Location of CNV (eyes)					
Subfoveal	24	16	17	15	
Juxtafoveal	8	3	2	5	0.94*
Extrafoveal	5	1	2	2	
Baseline BCVA (logMAR)	0.54±0.36	0.72±0.37	0.59±0.44	0.67±0.60	0.57†
No. of treatment/year	1.9±1.3	1.3±0.6	N/A	N/A	N/A
Follow-up period (months)	19.5±5.6	19.1±7.7	19.3±7.4	22.4±4.2	0.95†

Values are presented as mean±SD, except for gender and location of CNV.
*χ^2 test; †Kruskal–Wallis test.
BCVA, best-corrected visual acuity; BP, oral bisphosphonates; CNV, choroidal neovascularisation; logMAR, logarithm of the minimum angle of resolution; PDT, photodynamic therapy; VEGF, vascular endothelial growth factor.

data of the enrolled patients. The visual acuities were determined using a Landolt C chart and were converted to a logarithm of the minimum angle of resolution (logMAR) for calculation and description. The central retinal thickness (CRT) was determined automatically by a 6 mm retinal map from Stratus OCT and by a 200×200 retinal map from Cirrus OCT.

In general, the patients were observed without treatment from May 2000 to March 2005 since no method of treatment except photocoagulation was available for mCNV during this period. PDT became available in Japan in June 2004, so this was the main intervention used for patients with mCNV from April 2005 to March 2009. The off-label use of bevacizumab was started in November 2008 and ranibizumab was available in Japan from April 2009. Anti-VEGF therapy was performed as needed starting from the initial treatment. However, since PDT and intravitreal injection of ranibizumab for mCNV were not covered by national health insurance in Japan, the patients were asked to pay for off-label use of bevacizumab or PDT or ranibizumab, or received observation without treatment as the first management at our hospital. In addition, from May 2008, oral BP was introduced as a tentative treatment for those patients who declined intravitreal injections of anti-VEGF drugs and PDT. The patients underwent monthly examination and if the lesion had not resolved after the initial treatment or recurrence of the lesion (recurrent CNV accompanied by subretinal haemorrhage or macular oedema detected by funduscopy or OCT), re-treatment was carried out. Fluorescein angiography and indocyanine green angiography were repeated, as needed, at the discretion of the investigators. For re-treatments, the treatment initially selected was used again whenever possible. Re-treatments were performed with at least 1 month's interval for anti-VEGF treatment and at least 3 months' interval for PDT.

In the BP group, 5 mg/day of oral alendronates (Teijin Pharma, Tokyo, Japan) was preferably prescribed, but the use of 35 mg/week was allowed according to patients' compliance, for 2 years. Patients were informed about the side effects of BP (eg, gastritis, arthralgia, uveitis) and were advised to consult their doctor if they had any unusual symptoms. Medication compliance was checked by interview at the monthly examination. Booster treatment using intravitreal bevacizumab was allowed if a deterioration of the mCNV lesion (increase or recurrence of subretinal haemorrhage or macular oedema) accompanied by a decrease of best-corrected visual acuity (BCVA) from the last visit was seen.

LogMAR BCVA was evaluated as the main outcome of treatment. The change in CRT was also assessed over the treatment period. Each patient was measured by the same OCT instrument whenever possible throughout the follow-up period. In certain cases 60 μm was subtracted from each CRT value measured with the Cirrus OCT to obtain CRT values similar to those measured with a Stratus OCT.[17] In the no-treatment group, we could not obtain sufficient OCT data as the instruments were unavailable.

For statistical analysis, the χ^2 test, paired t test, unpaired t test, or Kruskal–Wallis test, whichever was the most appropriate, was performed to compare any two groups. A repeated-measures analysis of variance was used to compare changes in the BCVA between the BP, PDT, anti-VEGF and non-treatment groups over 24 months of follow-up. p Values <0.05 were considered to be statistically significant.

All interventions in this study were performed under approval by the Kobe University institutional review board and informed consent from all the patients.

RESULTS

Fifteen eyes of 13 patients with mCNV treated with BP were followed up for 24 months, since three cases stopped visiting the hospital (two eyes of one patient at 9 months, two eyes of one patient at 15 months and one eye of one patient at 21 months) and one patient discontinued medication after 3 months because of bilateral uveitis, which resolved with topical steroids.

The mean BCVA of the patients was maintained up to 24 months in the BP and PDT groups, while that of no-treatment group was significantly worse during 24 months of follow-up ($p=0.013$). In the BP group, the mean BCVA change from baseline to the last visit in discontinued cases was −0.17±0.48 logMAR units. Four eyes of four patients (19% of total eyes and 24% of total patients) in the BP group required booster treatment five times over 24 months of follow-up (an average of 1.3 times for those eyes needing booster treatment, and 0.2 times for each eye in the entire BP group). One of the patients who dropped out received a booster treatment during the follow-up period (21 months).

The mean BCVA of the patients in the anti-VEGF group was significantly improved from baseline 12 months after the initial treatment ($p=0.011$), but the change was not significant at 24 months ($p=0.14$) (figure 1). The mean BCVA changes in the BP, PDT and anti-VEGF groups were significantly better than

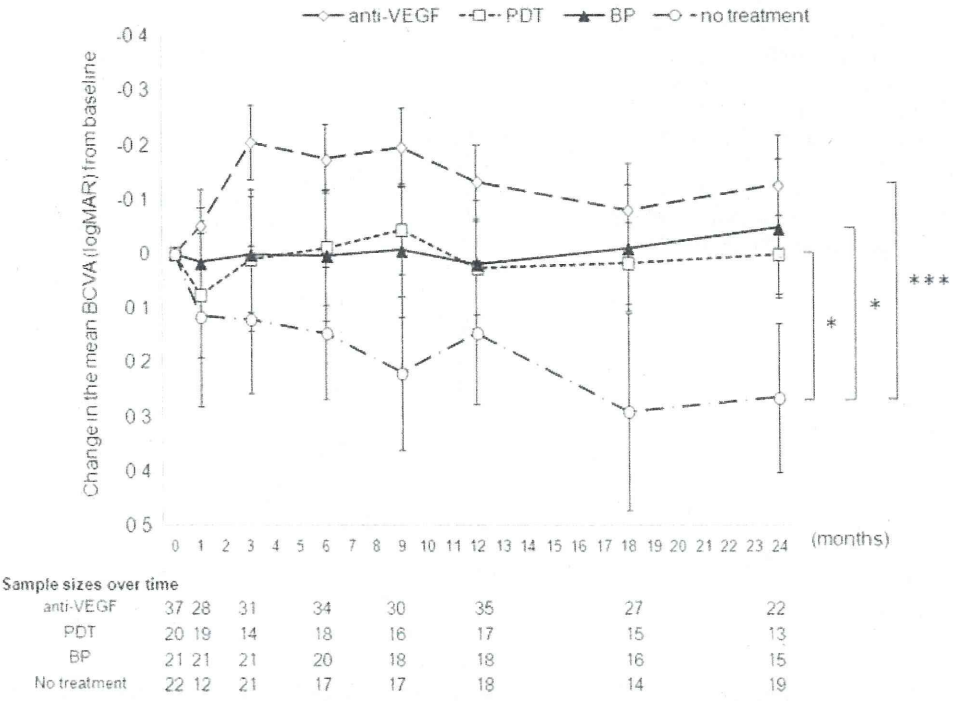

Figure 1 Time-course of the logMAR BCVA values with oral bisphosphonates. The values are presented as means ±SEM. *p<0.05, ***p<0.0005. BCVA, best-corrected visual acuity; BP, oral bisphosphonates; logMAR, logarithm of the minimum angle of resolution; PDT, photodynamic therapy; VEGF, vascular endothelial growth factor.

that in the no-treatment group over 24 months of follow-up (p=0.032, 0.021 and 0.0004, respectively).

To exclude the influence of bilateral cases on the results in the BP group, we repeated the statistical analysis excluding the data of the left eye in four bilateral cases and again found a significant difference between the BP and control groups (p=0.039). The proportions of cases in which BCVA improved >0.3 logMAR, showed changes between −0.3 to 0.3 logMAR and deteriorated more than 0.3 logMAR (−0.3 logMAR) from baseline to 24 months after treatment are shown in figure 2. The results suggest a relatively better outcome in the anti-VEGF group (more patients gained vision and fewer patients lost vision compared with other treatments) and equivalent results in the BP and PDT groups. The mean foveal thickness measured by OCT was significantly decreased in the BP, PDT and anti-VEGF groups (p=0.0025, 0.042 and 0.00082, respectively) (figure 3). No adverse systemic side effects were found or self-reported in any of the cases. Detailed findings from a selected patient in the BP group are shown in figure 4.

DISCUSSION

This study has shown that oral BP can maintain the vision of patients with mCNV for 2 years. The effect was almost equivalent to that of PDT monotherapy. Although anti-VEGF monotherapy, as needed, showed a significant improvement in visual

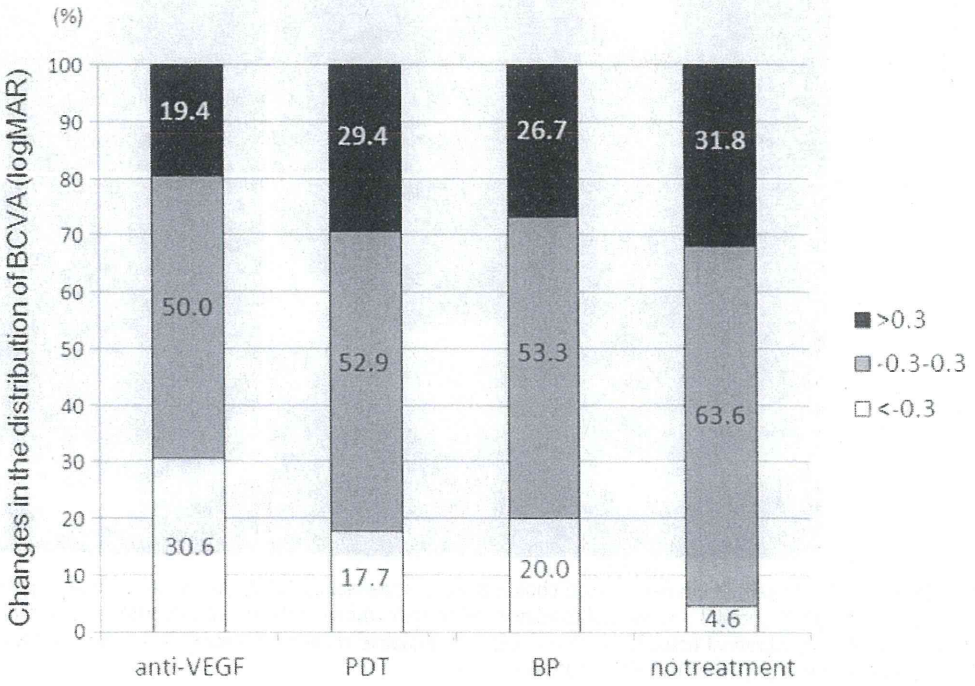

Figure 2 Chronological changes in the distribution of visual acuity in anti-vascular endothelial growth factor therapy, photodynamic therapy, oral bisphosphonate and no-treatment groups. Percentages are indicated in each column. BCVA, best-corrected visual acuity; BP, oral bisphosphonates; logMAR, logarithm of the minimum angle of resolution; PDT, photodynamic therapy; VEGF, vascular endothelial growth factor.

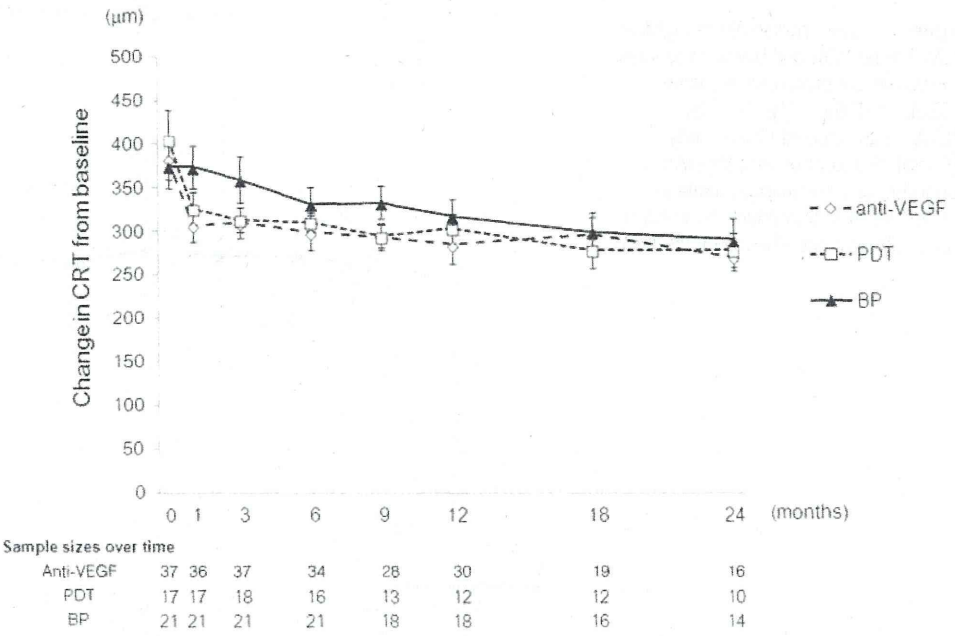

Figure 3 Time-course of the central retinal thickness with anti-vascular endothelial growth factor therapy, photodynamic therapy and oral bisphosphonates (BP). The values are presented as means±SEM. BP, oral bisphosphonate; CRT, central retinal thickness; PDT, photodynamic therapy; VEGF, vascular endothelial growth factor.

acuity at 12 months after treatment, the advantage was reduced at 24 months.

In our previous study, we found that oral BP stopped progression of CNV due to age-related macular degeneration and pathological myopia.[16] In that study BCVA was maintained for at least 6 months, and the measured lesion size was significantly reduced with treatment. In this report, we have further proved that oral BP can maintain the vision of patients with mCNV for up to 24 months. CNV due to pathological myopia is more often seen in middle-aged and older women than in men,[2] and osteoporosis is a representative age-related disorder for elderly women.[18] Hence, the female patients with these diseases are good candidates for oral BP. PDT with verteporfin, originally established to treat CNV due to age-related macular degeneration, was reported to have some benefits for mCNV at the 1 year outcome.[19] However, the effects did not persist beyond

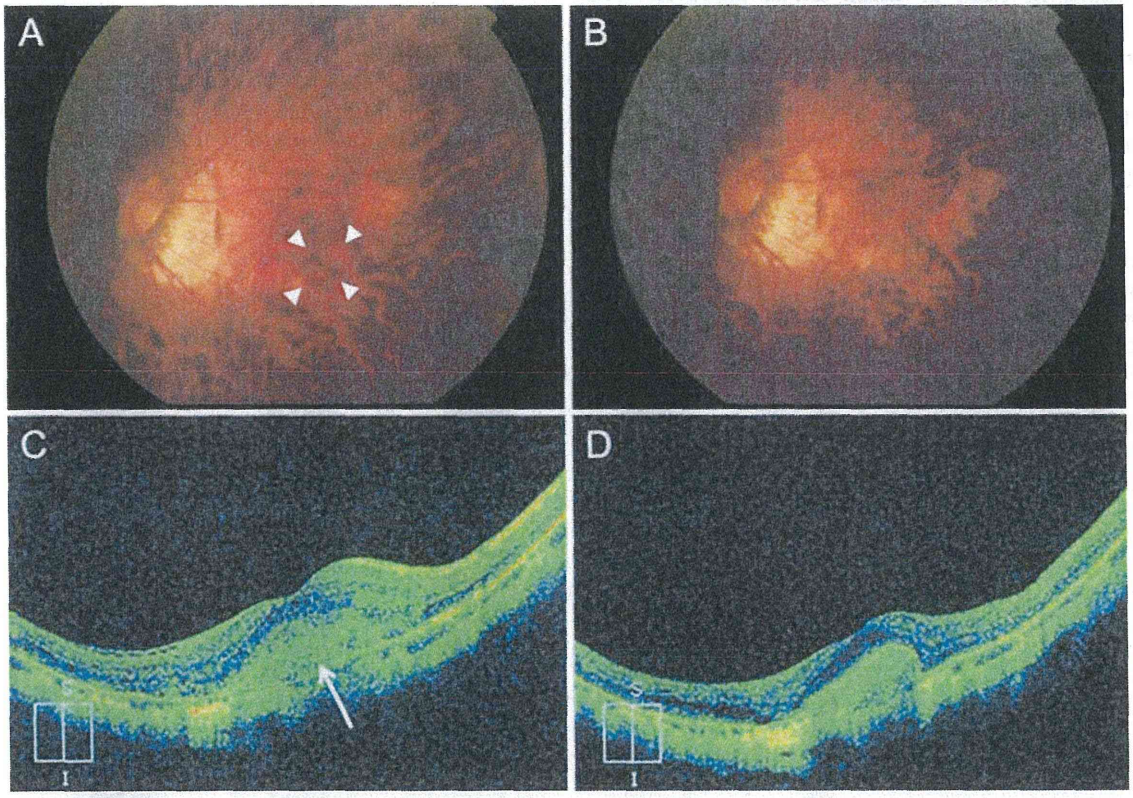

Figure 4 A 72-year-old woman showed choroidal neovascularisation (CNV) (arrow heads) due to pathological myopia (A). Optical coherence tomography (OCT) showed a subretinal exudative lesion (arrow) before treatment (C). After oral administration of alendronate for 2 years, the CNV became fibrotic subretinal tissue (B) with no apparent exudative change seen using OCT (D). Her best-corrected visual acuity improved from 20/60 at baseline to 20/30 at 24 months after treatment.

2 years.[20] Moreover, neither intravitreal injections of anti-VEGF antibodies nor PDT is suitable for prevention of the disease. Hence, recent reviews have pointed out the need for an optimal strategy for maintaining vision after induction therapy with anti-VEGF agents.[21] We suggest that oral BP might be useful for this purpose.

Autoradiography with an intraperitoneal administration of [^{14}C]alendronate in mice showed that it accumulates in bone tissue, and also in the eye,[22] particularly in the choroidal tissues (personal communication with Teijin Pharma, 2010). This may explain the delivery of oral alendronates to CNV lesions. Alendronate is a nitrogen-containing bisphosphonate (N-BP) which inhibits famesyl diphosphonate synthase in the biosynthetic mevalonate pathway. Reports have shown that N-BP inhibits the expression of VEGF, matrix metalloproteinase and the integrin families, thus restricting angiogenesis both in vitro and in vivo.[9 15] The involvement of matrix metalloproteinase, integrins and VEGF in CNV formation has been well documented.[23] Alendronate may suppress CNV via a direct inhibition of the proliferation of vascular endothelial cells,[24] and by regulating cellular angiogenic gene expression.[15 25]

Hence, we considered that the effects of oral BP should be further investigated as a therapeutic drug for CNV, including pathological myopia. Oral BP could be used as a monotherapy to stabilise the vision of patients with mCNV. Moreover, the use of oral BP after anti-VEGF treatment should be examined as a possible treatment for CNV since it might reduce the number of anti-VEGF treatments required.

Owing to the small sample size and non-randomised nature of the study, a definitive conclusion cannot be drawn from these results, and further studies including a randomised controlled trial are required to confirm the safety and efficacy of BP in the eye. Since this is a pilot study we did not perform statistical correction for multiple comparisons, which might be another limitation of the study. Our goal is to determine whether BP are useful as preventative or supportive drugs for anti-VEGF use in CNV treatment. This study provides a new insight into the use of this drug class in ophthalmology, and suggests a new possibility for the management of CNV accompanied by pathological myopia.

Contributors Substantial contributions to conception and design: SH; acquisition of data: AM, SH, TN, YT; analysis and interpretation of data: AM, SH, AN; drafting of the article: AM, SH; revising the article critically for important intellectual content: TN, YT, AN; final approval of the version to be published: AM, SH, TN, YT, AN.

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Competing interests None.

Patient consent Obtained.

Ethics approval Kobe University institutional review board.

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CLINICAL INVESTIGATION

Visual outcome of photodynamic therapy for typical neovascular age-related macular degeneration and polypoidal choroidal vasculopathy over 5 years of follow-up

Akiko Miki · Shigeru Honda · Hiroshi Kojima · Masaya Nishizaki · Tomoko Nagai · Masashi Fujihara · Mamoru Uenishi · Mihori Kita · Yasuo Kurimoto · Akira Negi · Hyogo Macular Disease Study Group

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Abstract

Purpose To evaluate the long-term effects of photodynamic therapy (PDT) on typical neovascular age-related macular degeneration (tAMD) and polypoidal choroidal vasculopathy (PCV).

Methods This was a multicenter prospective study of 139 eyes from 136 patients (tAMD: 74 eyes; PCV: 65 eyes) who underwent PDT as the initial treatment. The change in best-corrected visual acuity (BCVA), predictive factors for the BCVA at 60 months, frequency of recurrence, and mean recurrence period were analyzed.

Results The pre-PDT BCVA and greatest linear dimension (GLD) did not differ between the two groups. The mean BCVA (logMAR) was significantly improved at 6 months post-initial PDT (post-PDT) in the PCV group (−0.11, $P = 0.0091$). However, at 60 months post-PDT, the mean BCVA was significantly worse than baseline in the tAMD (+0.21, $P = 0.0035$) and PCV (+0.21, $P = 0.0076$) groups. Pre-PDT BCVA, age, and GLD were the factors significantly associated with the BCVA at 60 months post-PDT. Although the frequency of recurrence did not significantly differ between the two phenotype groups, the mean recurrence period was significantly longer in the PCV group than in the tAMD group (15.7 vs. 8.6 months, $P = 0.0020$).

Conclusions PDT may not have benefits for visual acuity in cases of tAMD and PCV over 5 years of follow-up.

Keywords Long-term outcome · Photodynamic therapy · Age-related macular degeneration · Polypoidal choroidal vasculopathy · Multicenter study

A. Miki · S. Honda (✉) · A. Negi
Department of Surgery, Division of Ophthalmology, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan
e-mail: sighonda@med.kobe-u.ac.jp

H. Kojima · Y. Kurimoto
Department of Ophthalmology, Kobe City General Hospital, Kobe, Japan

M. Nishizaki
Department of Ophthalmology, Ono Municipal Hospital, Ono, Japan

T. Nagai
Department of Ophthalmology, Steel Memorial Hirohata Hospital, Himeji, Japan

M. Fujihara · M. Uenishi
Department of Ophthalmology, Mitsubishi Kobe Hospital, Kobe, Japan

M. Kita
Department of Ophthalmology, Hyogo Prefectural Amagasaki Hospital, Amagasaki, Japan

Present Address:
M. Kita
Department of Ophthalmology, National Hospital Organization Kyoto Medical Center, Kyoto, Japan

Introduction

Age-related macular degeneration (AMD) is one of the major causes of irreversible blindness in the elderly population in industrial countries [1]. In particular, the exudative type of AMD has a serious prognosis that is the main focus of current clinical management. Exudative AMD can be subcategorized into the following phenotypes. Typical neovascular AMD (tAMD) exhibits netlike choroidal neovascularization (CNV) in the subretinal and subretinal pigment epithelial spaces [2]. Polypoidal choroidal

vasculopathy (PCV) has been described as the second phenotype of exudative AMD and has a characteristic orange-colored protrusion on funduscopic examinations [3, 4]; it shows a polyplike pooling of the dye on indocyanine green angiography (ICGA) [4–7]. PCV accounts for about 8–13 % of white and over 50 % of Japanese patients diagnosed with exudative AMD [5, 8]. Retinal angiomatous proliferation (RAP) is thought to be the third phenotype of AMD and exhibits angiomatous juxtafoveal neovascularization originating from the retinal vessels [9]. RAP is less frequent than tAMD or PCV in the Japanese population [8] but shows a worse prognosis owing to the ineffectiveness of conventional treatments [10, 11].

Photodynamic therapy (PDT) with verteporfin and intravitreal injection of antivascular endothelial growth factor (VEGF) agents are currently the treatments of choice for exudative AMD [1]. Studies from Western countries have reported significantly better visual outcomes with monthly intravitreal injections of ranibizumab (IVR) than with PDT in exudative AMD patients [12, 13], but these studies did not distinguish between the phenotypes of AMD within the study. In addition, the effectiveness of IVR for AMD has not been well investigated in the Japanese population in which PCV is the major phenotype of exudative AMD [8], and the effects of anti-VEGF therapy for PCV differ from those for typical neovascular AMD (tAMD) [14]. Moreover, recent publications have reported that the effects of anti-VEGF therapy for PCV were limited [15–17]. In contrast, PDT has been shown to be more beneficial for PCV than for tAMD [18–23] over 24 months after the initial treatment. However, the long-term effectiveness of PDT on these AMD phenotypes remains unclear. In this study, we prospectively observed the outcomes of PDT in both AMD phenotypes (tAMD and PCV) over a 5-year follow-up period.

Participants and methods

Six institutions in Hyogo Prefecture, Japan, participated in this prospective study. All consecutive unrelated Japanese patients treated with PDT were recruited at the departments of ophthalmology of the participating hospitals from July 2004 through March 2006. Pegaptanib and ranibizumab were not then available in the country (they became available from 2009); hence, the selection bias was likely very small at the inclusion.

All patients received detailed ophthalmic examinations, including visual-acuity measurements, slit-lamp biomicroscopy, color fundus photography, optical coherence tomography (OCT), fluorescein angiography (FA), and ICGA. The differential diagnoses of tAMD and PCV were made in accordance with a previous report [8]. Briefly, the tAMD group included those cases with images of clear CNV networks without PCV on ICGA. The PCV cases in the present study showed subretinal reddish-orange protrusions corresponding to the choroidal origin of the polypoidal lesions, typically with the vascular networks in the posterior poles on ICGA. Patients with high myopia (axial length of more than 26.5 mm) or with histories of retinal vessel occlusion or uveitis were excluded.

In total, 246 eyes from 242 patients (tAMD: 139 eyes; PCV: 107 eyes) were initially recruited [22]. However, 139 eyes from 136 patients (tAMD: 74 eyes; PCV: 65 eyes) were finally followed up for more than 60 months after the first PDT owing to discontinued visits to the hospital (dropout ratio of 44 % over 5 years). This dropout ratio was likely lower than that in the TAP Extension study, in which 320 AMD patients treated with PDT and followed up for 2 years were subjected to extended follow-up, and of whom 193 patients completed an additional 3 years of follow-up (dropout ratio of 40 % over 3 years) [24]. The dropout ratios of the tAMD group (65/139, 47 %) and the PCV group (42/107, 39 %) did not differ significantly ($P = 0.29$, chi-square test).

All patients underwent standard PDT procedures as previously described [25, 26]. The lesion status was assessed every 3 months, and the treatments were performed again when serous retinal detachment, hemorrhage, or macular edema was recognized by funduscopy or OCT accompanied by a leakage on FA or when a defined lesion was observed on ICGA [25, 26]. No patients in this study underwent any therapy other than PDT until 24 months after the initial treatment. Thereafter, the choice of treatment modality was not fixed, and some patients received anti-VEGF drugs and/or steroid therapy (3 eyes in the tAMD group and 7 eyes in the PCV group), laser photocoagulation (2 eyes in the PCV group), and vitrectomy for vitreous hemorrhage (1 eye in the tAMD group and 2 eyes in the PCV group) at the discretion of the investigators. To determine the number of treatments, we counted each therapy other than PDT as one treatment. However, we considered an induction therapy of ranibizumab (3 consecutive monthly injections of ranibizumab) as one treatment in accordance with the PrONTO study criteria [27].

The main outcome of this study was the best-corrected visual acuity (BCVA) at 60 months post-PDT in the tAMD and PCV groups. The visual acuities were determined using a Landolt C chart and converted to logMAR values for calculation and description. To evaluate those factors useful for predicting the BCVA at 60 months post-PDT, multiple linear regression analyses were performed. The explanatory variables included sex, age, BCVA before treatment, GLD before treatment, and lesion phenotype (tAMD or PCV). Dummy variables were applied for sex (male = 1, female = 0) and lesion phenotype (tAMD = 1, PCV = 2).

We also analyzed recurrences after the last PDT to evaluate the recurrence period after the lesion had been resolved by PDT. A recurrence of the lesion was defined as a recurrence of any subretinal hemorrhage, serous retinal detachment, or increased retinal thickness accompanied by dye leakage on the FA or a defined CNV on ICGA [25, 26].

For statistical analysis, the chi-square test, two-tailed paired t test, or unpaired t test, whichever was the most appropriate, was performed to compare any two groups. Multiple regression analysis was performed using StatView version 5 software. The Kaplan-Meier analysis was performed with Statcel 2 add-in software (OMS Publishing, Saitama, Japan) for Windows Excel 2003. Probability values of 0.05 or less were considered significant.

This study was approved by the institutional review boards of the Kobe University Graduate School of Medicine and all participating clinical centers and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Results

The data summary for each phenotype (tAMD and PCV) is shown in Table 1. No significant difference in the pretreatment parameters was found between the two groups. The mean (SD) BCVA (logMAR) was significantly improved at 6 months after the initial PDT in the PCV group (-0.11 ± 0.44, corresponding to $+1.1$ lines in visual acuity score; $P = 0.0091$). The PCV group achieved a significantly greater improvement in the mean BCVA than did the tAMD group at 6 and 12 months after the initial PDT ($P = 0.0043$ and 0.013, respectively). However, the mean BCVA gradually deteriorated after 12 months post-initial PDT and became significantly worse than baseline after 42 months in the tAMD group and after 48 months in the PCV group (Fig. 1). At 60 months post-initial PDT, the mean BCVA (logMAR) had significantly deteriorated from that of the corresponding pre-PDT value in the tAMD ($+0.21 \pm 0.58$, $P = 0.0035$) and PCV ($+0.21 \pm 0.59$, $P = 0.0076$) groups (Fig. 1). If we excluded those patients who received any therapy other than PDT during the follow-up period, the change in mean BCVA was $+0.20 \pm 0.59$ in the tAMD group ($n = 70$) and $+0.17 \pm 0.60$ in the PCV group ($n = 54$), which were also significantly worse ($P = 0.0071$ and 0.048, respectively). With regard to the distribution of the BCVA values, the proportion of good BCVA (≥ 0.4 decimal VA) was decreased at 60 months post-PDT as compared to baseline in both phenotypes, and the proportion of poor BCVA (≤ 0.01 decimal VA) increased significantly during the same time period in the tAMD and PCV groups ($P = 0.019$ and 0.037, respectively; Fisher's exact test) (Fig. 2), which resulted in a deterioration in the mean BCVA in the tAMD and PCV groups. Multiple linear regression analyses demonstrated that the pretreatment BCVA, age, and GLD were the predictive factors significantly associated with the BCVA at 60 months post-PDT (Table 2).

Patients received 2.6 ± 1.3 (mean ± SD) and 2.7 ± 1.5 treatments in the tAMD and PCV group, respectively, during the 60 months of follow-up, which did not differ significantly ($P = 0.81$). In the present study, the condition recurred in 56 of 139 eyes (40 %) in the tAMD cases and in

Table 1 Data summary of participants stratified by AMD phenotype

	tAMD ($n = 74$)	PCV ($n = 65$)	P value
Age (years)	73.2 ± 9.2	71.7 ± 7.3	0.27*
Sex (M/F)	49/24	46/17	0.46□
GLD (l m)	3844 ± 1562	3579 ± 1273	0.28*
Median pre-PDT BCVA, decimal VA (range)	0.2 (0.01–0.6)	0.25 (0.01–0.8)	
Mean pre-PDT BCVA, logMAR	0.87 ± 0.48	0.71 ± 0.44	0.053*

Values represent means ± SDs except for those for sex and median pre-PDT BCVA

tAMD typical neovascular age-related macular degeneration, *PCV* polypoidal choroidal vasculopathy, *GLD* greatest linear dimension, *pre-PDT BCVA* best-corrected visual acuity before photodynamic therapy

* Unpaired t test

□ Chi-square test

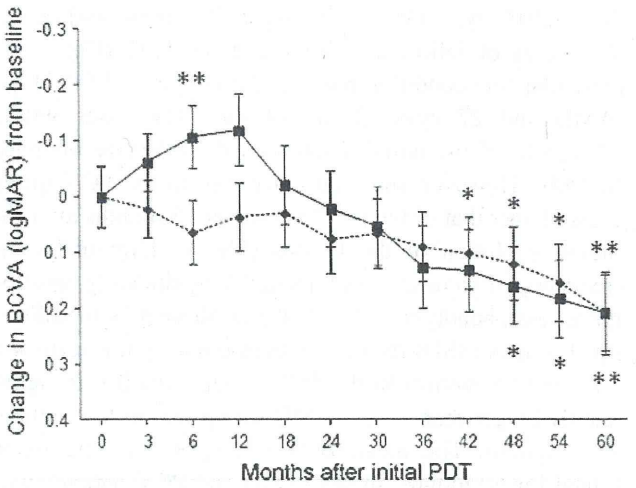

Fig. 1 Mean changes in BCVA from baseline in tAMD and PCV patients followed up for 60 months after initial PDT. The BCVA was determined using a Landolt C chart and converted to logMAR values for calculation and presentation. Rhombus with dashed line: tAMD; square with solid line: PCV. Values are presented as means ± SEMs. *P < 0.05, **P < 0.01 compared with baseline

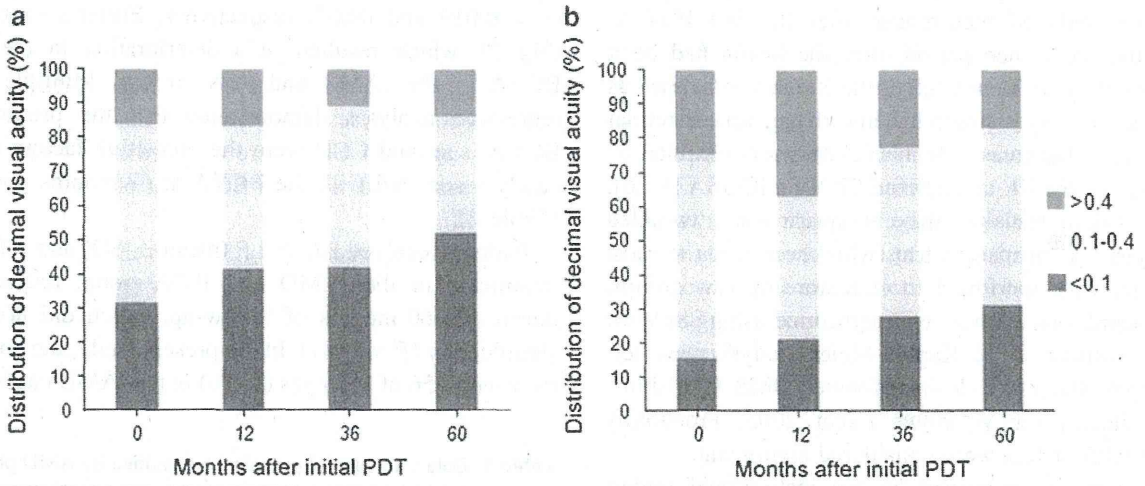

Fig. 2 Chronological changes in the distribution of visual acuity in tAMD (**a**) and PCV (**b**) patients followed up for 60 months after initial PDT

Table 2 Multiple regression analysis of preoperative variables and BCVA at 60 months after initial PDT

	CR	SE	*R*	*P* value
Age	0.021	0.006	0.29	0.0004
Sex (male = 1, female = 0)	−0.158	0.10	−0.12	0.12
Pre-PDT BCVA, logMAR	0.382	0.097	0.30	0.0003
GLD	9.42(E−5)	3.25(E−5)	0.23	0.0045
Lesion phenotype (tAMD = 1, PCV = 2)	−0.061	0.094	−0.05	0.52

CR coefficient of regression, *SE* standard error, *R* standard partial correlation coefficient, *Pre PDT BCVA* best-corrected visual acuity before PDT,*GLD* greatest linear dimension

52 of 107 eyes (49 %) in the PCV cases during the 60 months of follow-up after the initial PDT (Fig. 3). In particular, the condition recurred in 44 eyes (32 %) of the tAMD and 27 eyes (25 %) of the PCV cases within 12 months of the initial resolution of the lesions obtained by PDT. However, the recurrence rate in the PCV group crossed over that of the tAMD group at 15 months after the initial resolution of the lesions (Fig. 3). Eventually, the frequency of recurrence did not differ significantly between these two phenotypes ($P = 0.49$) at 60 months of follow-up. The mean (SD) recurrence period during this term was 15.7 ± 13.5 months in the PCV group, which was significantly longer than in the tAMD group (8.6 ± 9.3 months, $P = 0.0020$). The mean BCVAs (logMAR) were maintained for 60 months in the tAMD and PCV patients with no recurrence of the lesion ($P = 0.33$ and 0.73, respectively), while those of the patients with recurrence of the lesion significantly deteriorated over 60 months ($P = 0.0012$ and 0.0018, respectively) (Fig. 4).

Discussion

In this study, we investigated the long-term effects of PDT in tAMD and PCV phenotypes by measuring the BCVA at 60 months post-PDT to determine the durability of treatment. The PCV patients did not show better outcomes than the tAMD patients in terms of visual acuity but did show a significantly longer duration of the PDT effect.

Our previous studies demonstrated significantly better effects for PDT in PCV patients than in tAMD patients for up to 30 months of follow-up [22, 23]. However, observations over a longer term may alter the outcomes of the therapy in each phenotype, because AMD lesions often recur [22, 23, 28] and occasionally affect the patient's vision. Hence, we compared the 60-month effectiveness of PDT in tAMD and PCV patients, which revealed that the visual outcomes of PDT were almost equivalent for these two phenotypes at 60 months after the initial treatment. Despite the remarkable improvement in the BCVA values at 6 and 12 months after the initial PDT in the PCV group, the values began to deteriorate after 12 months post-initial PDT, mainly owing to the recurrence of lesions, including two cases of vitreous hemorrhage with massive subretinal hemorrhage. In contrast, the mean BCVA in the tAMD group gradually deteriorated to a significantly worse level at 42 months post-initial PDT. Eventually, both groups showed quite similar outcomes in the mean BCVA, which were significantly worse at 60 months than at baseline. However, it was noteworthy that the cases without recurrence maintained their vision over the 60-month follow-up period. In a previous study using multiple regression analysis, we showed that a better preoperative BCVA, younger age, smaller GLD, and the PCV phenotype were all beneficial factors for the BCVA at 12 months after the initial PDT [22]. The present study supports those previous